



Translation

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VCstsF263/84	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/FR2003/002298	International filing date (<i>day/month/year</i>) 21 juillet 2003 (21.07.2003)	Priority date (<i>day/month/year</i>) 23 juillet 2002 (23.07.2002)
International Patent Classification (IPC) or national classification and IPC G01N 33/50, 1/28, B01L 3/00		
Applicant COMMISSARIAT A L'ENERGIE ATOMIQUE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 19 février 2004 (19.02.2004)	Date of completion of this report 29 September 2004 (29.09.2004)
Name and mailing address of the IPEA/EP	Authorized officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002298

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

- ☐ the international application as originally filed.
- ☒ the description, pages 1-32, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.
- ☒ the claims, Nos. 1-59, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.
- ☒ the drawings, sheets/fig 1/8-8/8, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	1-56	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-56	NO
Industrial applicability (IA)	Claims	1-56	YES
	Claims		NO

2. Citations and explanations**1. Reference is made to the following document:**

D1: "Toxicity bioassay of heavy metals in water using *Tetrahymena pyriformis*" WATER RESEARCH 1973, vol. 7, no. 7, 1973, pages 951-961.

2. The subject matter of claims 1-56 is novel (PCT Article 33(2)). The prior art does not describe:

a method for reacting a cell with a reagent, including the following steps of:

- (a) depositing an aqueous drop containing said cell onto a substrate that has a hydrophobic planar surface and at least one means for receiving said aqueous drops, said means consisting of one or more hydrophilic areas;
- (b) covering said drop with a separation film through which gas can pass, which film prevents the drop from evaporating and is immiscible with the reagent; and
- (c) inserting said reagent into the aqueous drop.

The prior art likewise does not describe a device

for reacting a cell with a reagent, which device includes:

- (a) the substrate that has a planar surface, as described in point (a) above, and is covered with the separation film described in point (b) above;
- (b) means for depositing the aqueous drops containing the cells onto the surface of said substrate and underneath said film; and
- (c) a controlled-atmosphere chamber.

3. The subject matter of dependent claim 8 is inventive (PCT Article 33(3)).

- (a) D1, which is the closest prior art, describes a method for determining toxicity, including steps of contacting a cell suspension with a heavy metal, depositing a resulting sample onto the surface of a Petri dish and covering the drops of said sample with mineral oil to prevent the evaporation thereof.
- (b) There are two difference between the subject matter of claim 8 and D1:
 - (i) The step of contacting the cells with the reagent is carried out after the aqueous drop containing said cells has been covered with the separation film whereas, in D1, the cell cultures are inserted into a recipient that contains the reagent then drawn out again in order to be deposited in the Petri dish. This makes it possible to work with extremely small amounts of cells (up to one cell per drop) and

extremely small amounts of reagent. What is more, the method of the invention can be automated more readily because the two operations of depositing the drops onto the substrate and inserting the reagent into said drops can be automated easily and separately.

(ii) The substrate has hydrophilic receiving areas whereas the rest of the surface is hydrophobic. The technical effect of this difference is that the drop formed on such a substrate is spherical in shape (see, for example, figure 9) whereas the drop formed on a uniform surface, such as the surface of a Petri dish, is very spread out. A spherical drop is advantageous in that it promotes the generation of circumvolving movements (Marangoni effect) and these promote the reaction between the cell and the reagent.

In view of the closest prior art, the objective technical problem in the application is that of providing an enhanced method for reacting a cell with a reagent. The solution proposed is the method described in point 2 above. Such a solution is inventive because there is nothing in the prior art to indicate that technical features (i) and (ii) could lead to the technical effects described above and, as a result, enhance the method described in D1.

3.1 The presence of an inventive step cannot be accepted with respect to claims 1-7 and 9-56. The subject matter of said claims includes the use of the following as a separation film: organic solvents (claim 7), moisture-saturated air (claim 9), a

flexible solid film such as a polydimethylsiloxane or nitrocellulose film (claims 10 and 11), or a rigid honeycombed cover made of a porous material (claim 12). The claims do not specify that the organic solvent must not be water-miscible and a water-miscible organic film cannot, for very obvious reasons, constitute a separation film. Moisture-saturated air is not included in the definition of a separation film because it is a gas and, unlike a film, is not therefore a substance with well-defined spatial limitations. A flexible solid film does not appear to be capable of surrounding a microscopic aqueous drop in such a manner as to prevent the drop from evaporating. A rigid honeycombed cover made of a porous material is not a film but a special covering and does not, therefore, come within the specifications in the independent claim. For these reasons, some of the embodiments of the invention are not clear while others do not appear to be capable of solving one of the problems of the invention, i.e. the problem of preventing the aqueous drops from evaporating. As a result, the presence of an inventive step cannot be accepted.